Remarks

Claims 1-3, 42-43, and 115 are currently pending and stand rejected under 35 U.S.C. §103(a). New claims 150-158 are supported by the specification and do not contain new matter.[1]

I. 37 C.F.R. §1.75 Objection

The Office has objected to claims 124 and 125 under 37 C.F.R. §1.75 as being a duplicate of claim 115. Per the Office's suggestion, claims 124 and 125 have been cancelled making this objection moot.

II. 35 U.S.C. §103(a) Rejection

Reconsideration is requested of the rejection of claims 1-3, 42, 43, and 115 under 35 U.S.C. §103(a) in view of U.S. Patent No. 5,972,986 ('986 Patent) and Santos et al.[2]

Claim 1 is directed toward a method to treat or prevent a neoplasia disorder in a mammal. The method comprises administering to the mammal a therapeutically-effective amount of celecoxib, N–hydroxy-2,2-dimethy-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide and paclitaxel.

The '986 Patent discloses a class of methylsulfonylbenzene or sulfonamidebenzene cyclooxygenase-2 selective inhibitors that are described as being useful for "preventing and treating neoplasia" and in particular, "preventing and treating epithelial cell neoplasia."[3] According to the '986 Patent, their compounds may also be

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[1]See claim 43 or 44.

[2]Santos et al., (1997) Clinical & Experimental Metastasis 15(5):499-508, of which only the abstract was cited in Paper 9. As such, Applicants' comments detailed above regarding the disclosure of Santos et al. only reflect review of the abstract.

[3]U.S. Patent No. 5,972,986 , abstract.

used in co-therapies with any one of approximately 350 compounds described as "antineoplastic agents or other growth inhibiting agents."[4] But nowhere does the '986 Patent disclose or suggest a combination comprising celecoxib, N–hydroxy-2,2-dimethy-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide and paclitaxel, as required by the method of claim 1.

Santos et al. disclose that matrix metalloproteinases "are thought to play a role in processes essential for tumor growth, invasion, and metastasis."[5] According to Santos et al., the matrix metalloproteinase AG3340 (N-hydroxy-2,2-dimethy-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide) is an "efficacious compound against the Lewis lung carcinoma model."[6] Nowhere, however, do Santos et al. either disclose or suggest the use of AG3340 in combination therapy generally or in combination with celecoxib and paclitaxel for the treatment or prevention of a neoplasia disorder, as required by the method of claim 1.

In the absence of any disclosure of the combination employed in the method of claim 1, a *prima facie* case for obviousness is lacking.

The Office asserts that it would have been obvious to combine three compositions (i.e., celecoxib, paclitaxel and AG3340), each of which is disclosed in the prior art to be useful for same purpose, in order to form a fourth composition that is used for the very same purpose (i.e., treatment of neoplasia).[7] But the '986 Patent and Santos et al., taken singly or together, provide no basis for this conclusion.

If anything, the disclosure of the '986 Patent is actually away from a single composition comprising celecoxib, paclitaxel and AG3340. The '986 Patent discloses

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[4]Id., columns 12-14.

[5]Santos et al., abstract.

[6]Id., abstract.

[7]Paper 9 at page 4.

that there are certain classes of antineoplastic agents that may be combined with cyclooxygenase-2 inhibitors for the treatment of neoplasia. According to the '986 Patent,

> ...such antineoplastic agents fall into several major categories, namely, anti-biotic-type agents, alkylating agents, antimetabolite type agents and a category of *miscellaneous type agents*. ***Alternatively,*** other anti-neoplastic agents such as *metallomatrix proteases (MMP)*, SOD mimics...may be used.[8]

The '986 Patent then discloses a number of examples of specific drugs belonging to each "major category" and discloses that taxol is a member of the "miscellaneous type" category.[9] Because taxol and MMP are disclosed as **alternative embodiments** for combination therapy with a cyclooxygenase-2 inhibitor (i.e., "alternatively"), a skilled artisan is taught to either combine a cyclooxygenase-2 inhibitor and taxol **or** a cyclooxygenase-2 inhibitor and a MMP. Contrary to the Office's assertion, a skilled artisan is not taught to combine a cyclooxygenase-2 selective inhibitor (i.e., celecoxib) a miscellaneous type antineoplastic agent (i.e., paclitaxel) and a MMP (i.e, AG3340) to arrive at the composition employed in the method of claim 1.

Furthermore, among the many compounds and classes of compounds the '986 Patent and Santos et al. propose, neither the '986 Patent nor Santos et al. offer any guidance that would have enabled a skilled artisan to prepare the combination employed in the method of claim 1. The '986 Patent discloses approximately **100** cyclooxygenase-2 selective inhibitors and state that any one of them may be co-administered along with any one of approximately **350** compounds described as

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[8]U.S. Patent No. 5,972,986, column 12, lines 50-60 (emphasis added).

[9]U.S. Patent No. 5,972,986, column 14, line 63.

"antineoplastic agents."[10] But no significance is placed on any particular combination of a cyclooxygenase-2 inhibitor and antineoplastic agent that would motivate one skilled in the art to select celecoxib from the 100 disclosed cyclooxygenase-2 inhibitors and further select paclitaxel from the 350 disclosed "antineoplastic agents." Moreover, of the 350 compounds described as "antineoplastic agents," the '986 Patent fails to even disclose AG3340 on its rather exhaustive list of co-therapy candidates. Santos et al. merely disclose the use of AG3340 as a potential agent for the treatment of lung cancer. They **do not** disclose or suggest using AG3340 in combination with any other agents. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select celecoxib and paclitaxel disclosed in the '986 Patent and combine it with AG3340 disclosed in Santos et al. to form a composition for use in treating a neoplasia disorder, as required by the method of claim 1. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of the '986 Patent and Santos et al. Claims 2, 3, 42, 43 and new claims 150-158, which all depend from claim 1, are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements they introduce.

Moreover, claim 115 is also not obvious in view of the cited art. Claim 115 is directed toward a composition comprising celecoxib, N–hydroxy-2,2-dimethy-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide and paclitaxel. As detailed above, the use of a composition comprising celecoxib, N–hydroxy-2,2-dimethy-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide and paclitaxel in a method to treat a neoplasia disorder is patentable over the '986 Patent and Santos et al. The

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[10]U.S. Patent No. 5,972,986, columns 5-8 and 12-14.

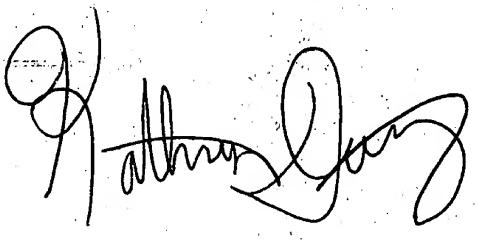
composition of claim 115 comprises the same components as the composition employed in the method of claim 1. For all of the reasons detailed with respect to claim 1, therefore, the composition of claim 115 is patentable in view of the '986 Patent and Santos et al.

III. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The examiner is invited to contact the undersigned attorney should any issues remain unresolved.

It is believed that no fees are due in connection with this Amendment B. If, however, the Commissioner determines a fee is due, he is hereby authorized to charge said government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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